

PATENT SPECIFICATION

1,195,200

BA

NO DRAWINGS.

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COMPLETE SPECIFICATION.

Pharmaceutical Compositions.

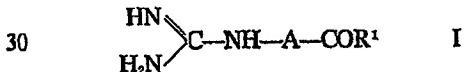
We, HORLICKS PHARMACEUTICALS LIMITED, a British Company, of Orchard Lea, Winkfield, Windsor, Berkshire, do hereby declare the invention, for which we pray that a 5 patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pharmaceutical 10 compositions having hypoglycaemic activity.

Diabetes mellitus is a relatively common disease which is characterised by hyperglycaemia and appears to result from an insufficiency of or inadequate utilisation of 15 the protein substance insulin. In fully developed cases, the pancreas appears to produce insufficient insulin to allow glucose to be utilised by muscle and insulin is commonly administered parenterally to assist 20 clearance of the high glucose blood levels which otherwise tend to build up.

Our researches have indicated that a particular class of guanidino-alkanoic acids and derivatives thereof, defined more precisely 25 hereinafter, is effective in enabling insulin to assist glucose uptake into the body tissues and hence in controlling hyperglycaemia.

These guanidino derivatives possess the general formula



(where A is a straight or branched aliphatic chain having 1—8 carbon atoms and R¹ is a hydroxy group, a lower alkoxy group having 1—3 carbon atoms, an aralkoxy group, 35 an aryloxy group which may be substituted with a halogen atom or alkoxy group, an

amino group or a mono- or di-alkyl-amino or alkyleneimino group).

Our researches have shown that the guanidino alkanoic acids of formula I 40 (R¹=OH) improve glucose tolerance in man where this is abnormal and that appears to be brought about by assisting the transport of glucose from the blood into the liver. In many diabetics, particularly juvenile 45 diabetics when insulin is administered in the first instance, it acts predominantly by assisting the passage of glucose into the liver and only later when the patient is under better control does the insulin appear to function 50 in the periphery by assisting the clearance of glucose from the blood into muscles. On the other hand, the esters and amides of formula I (COR¹ = ester or amide) appear 55 to assist insulin in the clearance of glucose into the muscles.

While we do not wish to be bound by theoretical considerations, it is believed that the esters and amides of formula I may be converted physiologically into the free acids. However, in order to ensure uptake of glucose from the blood into the liver as well as peripheral uptake into muscular tissues it is 60 advantageous to administer a free acid of formula I together with an ester or amide of formula I. 65

According to the present invention, therefore, we provide pharmaceutical compositions for the treatment of hyperglycaemia containing one or more acids of general 70 formula I (in which A has the above meaning and R¹ is a hydroxy group), and/or physiologically acceptable salts therof with acids or bases, together with one or more esters or amides of general formula I (in 75 which A has the above meaning and R¹ is a

[REVERSE SIDE]

SEE CORRECTION SLIP ATTACHED

- lower alkoxy group having 1—4 carbon atoms, an aralkoxy group, an aryloxy group which may be substituted by a halogen atom or alkoxy group; an amino group or a mono- or di-alkylamino or alkyleneimino group) and/or physiologically acceptable acid addition salts thereof.
- The chain A is an alkylene chain preferably having at least 2, advantageously at least 3, carbon atoms and preferably having not more than 5, advantageously not more than 6, carbon atoms. Straight chains are preferred, for example, ethylene, *n*-propylene, *n*-butylene and *n*-pentylene.
- The group R¹, when alkoxy, is an alkoxy group having 1—3 carbon atoms since such lower alkoxy groups have been found to produce pronounced hypoglycaemic action and have an excellent ratio of desired activity to unwanted side effects (Therapeutic Ratio). The ethoxy group is preferred, especially when A is an *n*-propylene chain. Where R¹ is aryloxy or aralkoxy, these groups are preferably mono-nuclear.
- R¹ may, however, even more usefully be an amino group or a mono- or di-alkylamino group, e.g. a mono- or di-methyl, ethyl or propyl amino group. Mono-alkyl amino groups are preferred, especially the mono-methyl amino group. R¹ may also be an alkyleneimino group preferably having 5 or 6 carbon atoms in the ring, e.g. a pyrrolidino of piperidino group.
- The compound 4-guanidino-butryamide shows markedly low toxicity combined with relatively high activity, so that its therapeutic ratio is particularly noteworthy. In general, the amides of formula I show a better therapeutic ratio than the corresponding esters. Of the compounds of formula I in which R¹ is OH, 4-guanidino-butyric acid is particularly noteworthy. The most preferred compositions according to the invention therefore contain 4-guanidino butyric acid and/or salts thereof with acids or bases together with 4-guanidino butyramide and/or acid addition salts thereof.
- The acid addition salts of the compound of formula I include, for example, the hydrochlorides, hydrobromides, sulphates, nitrates, phosphates, acetates, propionates, maleates, citrates, tartrates, fumarates, and hydrocarbon-sulphonates such as *p*-toluenesulphonates.
- The salts with physiologically acceptable bases include alkali metal and alkaline earth metal salts as well as salts with physiologically acceptable amines, for example sodium, potassium, calcium, morpholine and piperazine. It is also possible for the acids of formula I to enter into salt formation with the esters and amides of formula I.
- The compositions according to the invention may be formulated in conventional manner and may contain a pharmaceutical carrier or excipient and are preferably in dosage unit form to facilitate prescription, for example in the form of tablets, effervescent tablets, pills, chewing gum, sachets, capsules, suppositories or ampoules of injectable liquid; each dosage unit preferably contains 5 to 1000 mg. of the acid component and also the ester or amide component, advantageously 10 to 500 mg., for example 20 to 400 mg.
- The injectable preparations may take the form of aqueous or oily solutions or suspensions. Suitable carriers or excipients for injectable preparations include for example, sterile pyrogen-free water, parenterally acceptable oils or other non-aqueous media or oil-containing emulsions, if desired containing one or more suspending, dispersing, stabilising, emulsifying, solubilising, preserving, or buffering agents. Buffered solutions are preferably in the physiological pH range 5—8, advantageously 6.5—7.
- The carrier in the solid oral forms may, for example, include gelatin, lactose, starch, talc, magnesium stearate, hydrogenated oils or polyglycols; effervescent tablets will include gas-generating agents such as bicarbonate and citric acid. Suppositories may contain a conventional suppository base, e.g. cocoa butter or polyglycols, with or without surface active agents.
- The compositions may also take the form of liquid oral preparations such as syrups, elixirs or emulsions, which may contain one or more suspending, emulsifying, stabilising or thickening agents together with suitable sweetening, flavouring, colouring or preserving agents. The concentration of active substance in these preparations is preferably from 0.5 to 20% by weight.
- Preparations for inhalation preferably take the form of aerosols containing, for example, conventional aerosol propellants, such as fluorohydrocarbons.
- Further compositions include powders or granules for reconstitution immediately before injection.
- The concentration of guanidino compounds in the solid compositions is preferably from 2.5 to 500 mg/ml advantageously 10 to 400 mg/ml.
- The daily dose level will in general be in the range 5 to 1000 mg. of the guanidino compounds, or even up to 3000 mg. The active compounds may for example be administered parenterally, rectally or, more preferably, orally. The active guanidino compounds may be administered in the form of the combined compositions according to the invention or separately.
- Injection is preferably intramuscular and the duration of action of the active compounds in the individual is preferably arranged to be 24 hours so that only a single daily injection is required.

Since the active components in the compositions according to the invention assist insulin in effecting glucose uptake, the compositions may usefully contain insulin as in 5 the compositions described in our copending

Application No. 52756/66 (Serial No. 1,195,199).

The following Examples are given by way of illustration only:—

| 10 | <i>Example 1</i> | TABLETS | <i>per tablet</i> |
|----|--|---------|-------------------|
| 15 | 4-Guanidino butyramide HCl ... | 500 g. | 250 mgm. |
| | 4-Guanidino butyric acid HCl ... | 500 g. | 250 mgm. |
| | Maize starch (dried) | 120 g. | 60 mgm. |
| 15 | Acacia (mucilage of 10% concentration) | 20 g. | 10 mgm. |
| | Lubricant | 60 g. | 30 mgm. |
| | <i>Formula of Lubricant</i> | | |
| 20 | Starch | 6 g. | |
| | Talc | 2 g. | |
| | Magnesium Stearate | 0.25 g. | |

Procedure

500 g. 4-guanidino butyramide hydrochloride and 500 g. 4-guanidino butyric acid hydrochloride are thoroughly mixed together with 120 g. maize starch in the dried state. 25 20 g. acacia is added (as a mucilage of 10% concentration) and mixed with the above. The mixture is granulated by passing through a No. 8 (B.P.) sieve. The granules so formed are dried in an oven or in a fluid bed dryer at 60°C. The dried granules are then passed through a No. 10 (B.P.) sieve. The granules are weighed and the required amount of lubricant added with thorough mixing. The mixture is finally pressed into tablets using an automatic tabletting machine. In some cases it is desirable that the tablets are enteric coated or sugar coated.

Example 2 TABLETS

| | parts by weight | 40 |
|-----------------------------------|-----------------|----|
| 4-Guanidino butyramide HCl ... | 250 | |
| 4-Guanidino butyric acid HCl ... | 250 | |
| Maize starch B.P. (dried) | 50 | |
| Talc B.P. | 8 | 45 |
| Magnesium stearate | 4 | |

The ingredients are mixed and compressed into large crude tablets $\frac{1}{2}$ " to 1" in diameter which are then broken up and passed through a No. 12 sieve. The resultant granules are mixed with lubricant (15 parts by weight of lubricant to 279 parts by weight of granules) and then compressed into tablets. The tablets may then be varnished and sugar coated.

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Example 3

DRY CAPSULES

per capsule

| | | | |
|----|----------------------------------|---------|----------|
| 60 | 4-Guanidino butyramide HCl ... | 100 gm. | 100 mgm. |
| | 4-Guanidino butyric acid HCl ... | 100 gm. | 100 mgm. |
| | Lubricant | 2 gm. | 2 mgm. |
| | <i>Lubricant Formula</i> | | |
| | Magnesium Stearate | 1 gm. | 1 mgm. |
| | Talc | 1 gm. | 1 mgm. |

Procedure

100 gm. of 4-guanidino butyramide HCl and 100 gm. of 4-guanidino butyric acid HCl are thoroughly mixed together with 2 gm. of lubricant. The resulting free flowing powder is filled directly into hard gelatine capsules, using a suitable dry capsule filling machine.

70 The procedure is also applicable for the preparation of capsules containing ad-

mixtures of the other active compounds described herein.

Alternatively the mixture of active compounds is passed through a No. 60 sieve and mixed with 3% of its own weight of a lubricant which may consist only of talc B.P. or a mixture of equal parts of talc B.P. and magnesium stearate. The mixture may then be filled into two-piece hard-shell gelatine capsules.

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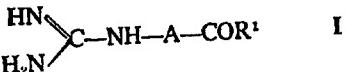
Example 4**AMPOULES**

**4-Guanidino Butyramide HCl and
4-Guanidino Butyric Acid HCl**

- 5 The 4-guanidino butyramide hydrochloride and 4-guanidino butyric acid hydrochloride may be dissolved in potable water distilled from a neutral glass or metal still fitted with an efficient device for preventing entrainment of droplets. The solution may be buffered within the physiological pH range using a Sorenson type phosphate buffer. It may also be made isotonic with blood serum by the addition of sodium chloride B.P. Chlorocresol B.P. may be added to the extent of 0.1% to effect preservation if required.
- 10 The solution may then be sterilised by filtration according to the British Pharmacopoeia, 1963, and filled into suitable sterile ampoules or vials. This procedure may also be employed for the preparation of ampoules of the guanidino-alkanoic acids with their ester and amide derivatives according to the invention.
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WHAT WE CLAIM IS:—

1. Pharmaceutical compositions for the treatment of hypoglycaemia containing as active material one or more acids of the general formula



- (in which A is a straight or branched aliphatic chain having 1—8 carbon atoms and R¹ is an hydroxy group) and/or physiologically acceptable salts thereof with acids or bases, together with one or more esters or amides of general formula I (wherein A has the above meaning and R¹ is a lower alkoxy group having 1—3 carbon atoms, an aralkoxy group, an aryloxy group which may be substituted with a halogen atom or alkoxy group; an amino group or a mono- or di-alkylamino or alkyleneimino group) and/or physiologically acceptable acid addition salts thereof.
- 35 2. Compositions as claimed in claim 1 in which A is an alkylene chain having 2—6 carbon atoms.
3. Compositions as claimed in claim 1 in which A is an alkylene chain having 3—5 carbon atoms.
- 40 4. Compositions as claimed in claim 1 in which A is an ethylene, n-propylene, n-butylene or n-pentylene chain.
5. Compositions as claimed in any of the preceding claims in which, where R¹ is an alkoxy group it is an ethoxy group.
- 45 6. Compositions as claimed in any of claims 1 to 4 in which R¹ in the amides of formula I is an amino or a mono- or di-
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methyl, -ethyl or -propyl amino group or a pyrrolidino or piperidino group.

7. Compositions as claimed in claim 1 in which the acid component is 4-guanidino butyric acid and the amide component is 4-guanidino butyramide.

8. Compositions as claimed in any of the preceding claims in which, where acid addition salts of the compounds of formula I are used, they are the hydrochlorides, hydrobromides, sulphates, nitrates, phosphates, acetates, propionates, maleates, citrates, tartrates, fumarates or p-toluene sulphonates.

9. Compositions as claimed in claim 1 in which the salts with bases of the acids of formula I are alkali metal, alkaline earth metal or amine salts.

10. Compositions as claimed in claim 1 in which the acid component is present in the form of a salt with the amide or ester component.

11. Compositions as claimed in any of the previous claims in the form of dosage units.

12. Compositions as claimed in claim 11 in which each dosage unit contains 5 to 1000 mg. of the acid component and 5 to 1000 mg. of the ester or amide component.

13. Compositions as claimed in claim 11 in which each dosage unit contains 10 to 500 mg. of the acid component and 10 to 500 mg. of the ester or amide component.

14. Compositions as claimed in claim 11 in which each dosage unit contains 20 to 400 mg. of the acid component and 20 to 400 mg. of the ester or amide component.

15. Compositions as claimed in any of the previous claims containing a pharmaceutical carrier or excipient.

16. Compositions as claimed in claim 15 in which the carrier or excipient includes sterile pyrogen-free water, a parenterally acceptable oil or oil-containing emulsion, if desired containing one or more stabilising, suspending, dispersing, emulsifying, solubilising, buffering or preserving agents; gelatin, lactose, starch, talc, magnesium stearate, a hydrogenated oil, a polyglycol, a gas-generating agent or a suppository base.

17. Compositions as claimed in any of claims 11 to 16 in the form of tablets, effervescent tablets, pills, chewing gum, sachets, capsules, suppositories or ampoules of injectable liquid.

18. Compositions as claimed in claim 1 in the form of syrups, elixirs or emulsions.

19. Compositions as claimed in claim 18 containing one or more suspending, emulsifying, stabilising, thickening, sweetening, flavouring, colouring and/or preserving agents.

20. Compositions as claimed in claim 18 or claim 19 containing from 0.05 to 20% by weight of active material.

21. Compositions as claimed in claim 125

- 1 in the form of aerosol spray compositions or powders or granules for reconstitution before injection.
22. Compositions as claimed in claim 1 substantially as herein described.
23. Compositions as claimed in claim 1 substantially as herein described with reference to any of the Examples.
24. A method of preparing compositions as claimed in claim 1 in which said acid component or salt thereof is admixed with said ester or amide component or salt thereof.

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